Supplemental Figure Legends

Supplemental Figure 1. Swim-stress induces KORp-ir in mouse brain. Representative images of KORp-ir in the nucleus accumbens (NAc), basolateral amygdala, and dorsal raphe (DRN) 30 min after mice were exposed to the swim-stress paradigm. Control sections show little KORp-ir as compared to Stress groups. NorBNI pretreatment (10 mg/kg) prior to swim-stress blocks the swim-stress-induced KORp-ir in all three brain regions. (Data are similar in hippocampal sections). All data are representative of 3-4 independent experiments.

Supplemental Figure 2. CRF injection causes KORp labeling in the mouse hippocampus and dorsal raphe nucleus. Top panels, Saline injected mice show no KORp-ir (green) in the CA3 region of the mouse hippocampus. However, 30 min after CRF injection (1 μg, i.c.v.) there was a robust increase in KORp-ir in the hippocampus that was blocked by pretreatment of mice with norBNI (10 mg/kg) 1 hr prior to injection of CRF. Bottom panels, saline injection caused no KORp-ir in the dorsal raphe. CRF injection caused an increase in KORp-ir in the dorsal raphe, which was also blocked by pretreatment with norBNI. Red channel is anti-GAD67.

Supplemental Figure 3. Putative series of events required for stress-induced dysphoria by activation of the KOR/dynorphin system. (1) Repeated exposure to

a stressor (in the present study this was either swim-stress or footshock) initiates (2) CRF or related peptide release, (3) which then activates CRF_2-R and subsequent dynorphin release (4). Dynorphin-activated KOR becomes phosphorylated by GRK3 (5) in the amygdala, dorsal raphe (DRN), nucleus accumbens (NAc), and hippocampus (Hippo). The specific sites responsible were not identified, but activation of KOR leads to the stress-induced dysphoria, as measured by aversion.